

Neomycin-Curare Neuromuscular Block and Reversal in Cats

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The cat sciatic-nerve-gastrocnemius-muscle preparation was used to study a) neuromuscular blocking potency of neomycin and curare, b) pharmacologic interaction of these drugs, and c) antagonism to neomycin-induced neuromuscular block. Curare was 100 times more potent than neomycin in producing neuromuscular block. The two drugs in combination were synergistic at doses causing more than 30 per cent depression of twitch response. Recovery from complete neomycin paralysis required 30 to 40 minutes and was accelerated by administration of calcium, 0.37 mEq/kg. Neostigmine was less effective in accelerating recovery. The combination of calcium 0.1 mEq/kg and sodium bicarbonate 1 mEq/kg was found to reverse neomycin paralysis effectively.

SINCE ITS INTRODUCTION in 1949, neomycin has been widely used orally for intestinal antisepsis, topically for treatment of superficial infections, and in body cavities for prevention and treatment of infections. Early investigations with neomycin in animals revealed that acute toxicity was manifest by respiratory arrest. Prolonged postoperative apnea in man following intraperitoneal neomycin, first reported by Pridgen in 1956,¹ was shown to be the result of neuromuscular block in 1958.² Neomycin neuromuscular block is potentiated by diethyl ether and such neuromuscular blockers as *d*-tubocurarine, succinylcholine and gallamine, but the extent and the type of pharmacologic interaction remains obscure.

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A series of laboratory investigations was done to compare the neuromuscular blocking potencies of neomycin and curare; to determine whether the two drugs interact; and to study the merits of various antagonists to the neuromuscular block produced by neomycin.

Methods

Thirty-seven healthy adult cats weighing 1.8 to 5.8 kg were anesthetized with intravenous injections of pentobarbital, 25 mg/kg. Cannulae were inserted into the trachea and the left femoral artery and vein of each cat; the right femoral condyle was transfixed with a 1/8-inch drill bit and the right knee and foot immobilized by attachment to a rigid frame. The tendon of the right gastrocnemius muscle was detached from the calcaneus and tied to an isometric force transducer § positioned so that the muscle had a constant resting load of 500 gm.

The right sciatic nerve was exposed in the midportion of the thigh, severed proximally, and placed on a bipolar stimulating electrode. The skin and muscles surrounding the electrode were suspended to form a well, which was filled with heavy mineral oil. The nerve was stimulated supramaximally every four seconds with a pulse of 4 msec duration (Block-Aid Monitor®, Burroughs-Wellcome & Company).

Arterial blood pressure was monitored with a liquid-phase transducer (Statham P-23AA). Arterial pressure and contractions of the gastrocnemius muscle were recorded on a two-channel, rectilinear, heat-writing recorder (Oscillator®, Texas Instruments). Respiration

§ The transducer is a compression, expansion, impedance type designed and built by the Department of Biomedical Engineering, University of Texas Southwestern Medical School at Dallas.

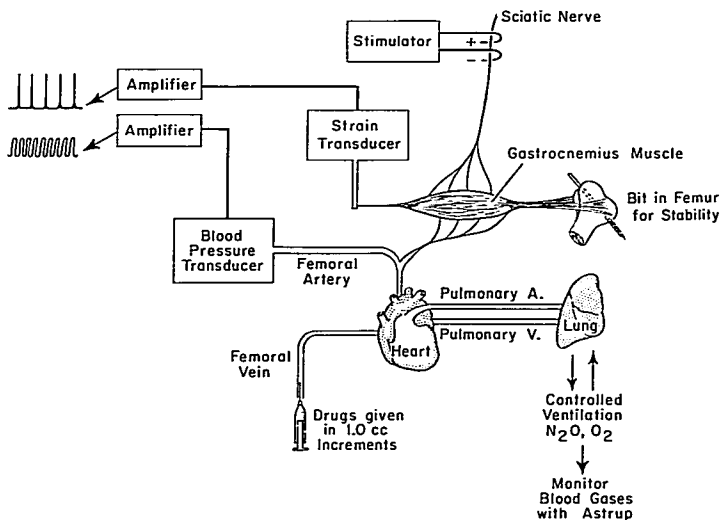


FIG. 1. Schematic representation of the experimental method. Reproduced by permission Giesecke *et al.*³

was controlled with a small-animal respirator (Harvard Respiration Pump) set to deliver 150 ml/kg/min at a rate of 20 breaths/min. Anesthesia was maintained with a 50 per cent mixture of nitrous oxide in oxygen delivered to the intake manifold of the respirator. Arterial blood was taken at intervals of 15 to 20 minutes and analyzed for pH, P_{CO₂} and P_{O₂} on an Astrup blood-gas analyzer (Radiometer). Respiratory alkalosis or acidosis was corrected by appropriate changes in respiratory volume. Metabolic acidosis was corrected with 7.5 per cent sodium bicarbonate according to the formula: mEq sodium bicarbonate = kg body weight × 0.2 × base deficit. Body temperature was maintained between 36 and 38 C by means of a heating pad.

All drugs were injected into the right femoral vein (fig. 1). The cats were divided into three groups:

A. Seven cats received *d*-tubocurarine in increments of 0.01 mg/kg at intervals of 2.5 minutes until the twitch response was extinguished.

B. Twenty-five cats received neomycin in increments of 5 mg/kg at intervals of 2.5 minutes until the twitch response was extinguished.

C. Five cats received *d*-tubocurarine, 0.03 mg/kg, plus neomycin, 3 mg/kg, every 2.5 minutes until the twitch response was extinguished.

The interval from the first dose of test drug to complete loss of twitch response was not longer than 30 minutes. The 25 cats in group B, paralyzed with neomycin, were used to study recovery. Five cats, serving as controls, were allowed to recover without pharmacologic interference. Five cats were given neostigmine, 0.08 mg/kg, and atropine, 0.02 mg/kg, one minute after complete paralysis with neomycin had been accomplished. Five cats were given calcium gluconate at three dosage schedules: 0.07 mEq/kg, 0.17 mEq/kg, and 0.37 mEq/kg. Five cats were given 7.5 per cent sodium bicarbonate, 1 mEq/kg. Five cats were given calcium gluconate, 0.11 mEq/kg, plus sodium bicarbonate, 1 mEq/kg.

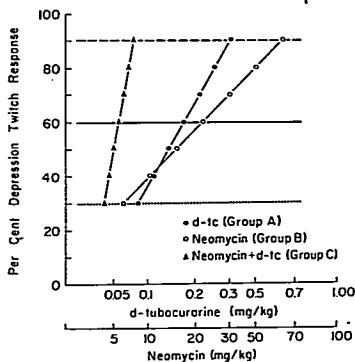


FIG. 2. Least square linear regression plot of the log-dose response curves for groups A, B, and C.

Log-dose response curves were plotted for each experiment and the linear portions of the curves for the groups were plotted by least-squares, linear regression. The results were analyzed by isobolograms.⁴ Recovery curves were plotted for each mode of therapy and compared with the control recovery curve.

Results

The log-dose response curves (fig. 2) show that at 40 per cent depression of twitch height, *d*-tubocurarine was 100 times more potent than neomycin in producing neuromuscular blockade. Therefore, in group C, the two drugs were given in combination, in a 1:100 ratio. The curve for group C experiments is shifted to the left and the slope is considerably steeper than the curves for groups A and B. Isobolograms were constructed at the 30, 60 and 90 per cent depression levels (fig. 3). The combination of *d*-tubocurarine and neomycin required to produce 30 per cent depression was found to lie on the 30 per cent isobole, suggesting additive drug action at 30 per cent depression. The combinations of doses required to produce 60 per cent and 90 per cent depression lay significantly below their respective isoboles, suggesting synergistic drug action at 60 per cent and 90 per cent depression.

The five animals which recovered unassisted regained 85 per cent of the pre-paralysis

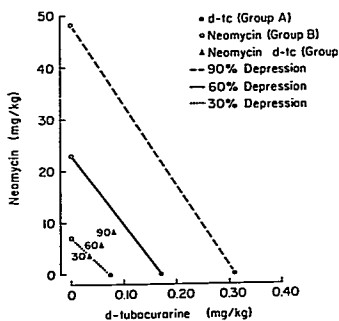


FIG. 3. Isobolograms constructed at 30, 60 and 90 per cent depression for *d*-tubocurarine on the horizontal axis (group A), neomycin on the vertical axis (group B), and combination of the drugs in a 1:100 ratio resulting in 30, 60 and 90 per cent depression (group C).

twitch response in 40 minutes (fig. 4). To facilitate comparison, the control curve appears as a background image in subsequent recovery curves. Utilizing the dosage recommended by Pittinger,⁵ five cats were given neostigmine, 0.08 mg/kg (fig. 5). Recovery appears to be accelerated below 60 per cent and delayed above 60 per cent, but the difference was not significant.

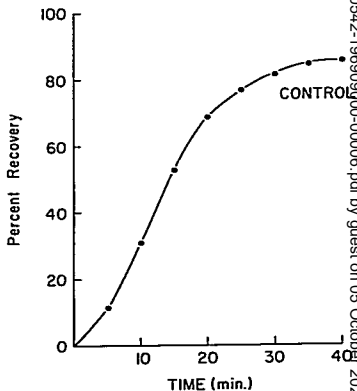


FIG. 4. Control recovery following total paralysis with neomycin in seven cats.

Calcium effectively reversed the paralysis produced by neomycin (fig. 6), but the optimal dose (0.37 mEq/kg) was considerably in excess of the usual clinical dose. Sodium bicarbonate accelerated partial recovery from profound paralysis; however, time to complete recovery was not changed significantly. The arterial pH was increased an average of 0.058 units by the sodium bicarbonate (fig. 7).

When calcium, 0.11 mEq/kg, was given shortly after sodium bicarbonate, 1 mEq/kg, recovery from neomycin paralysis was accelerated and compared favorably with that obtained by administering a higher dose of calcium (fig. 8).

Discussion

We recognize that significant redistribution, metabolism and excretion of the drugs may have occurred during the 30-minute period of the experiment.⁶ Reproducibility was obtained by maintaining a constant interval between drug doses and interventions. Recordings were continuous throughout the experiment.

Our data show that the combination of *d*-tubocurarine and neomycin was additive at 30 per cent depression of twitch response and synergistic at 60 per cent and 90 per cent depression. This phenomenon is due to the lack

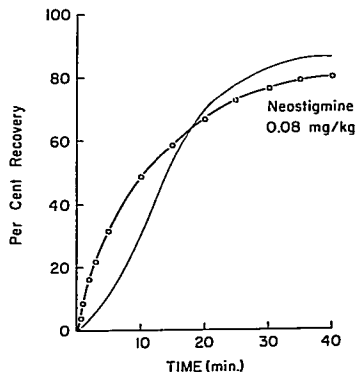


FIG. 5. Recovery from neomycin paralysis following the administration of neostigmine. The curve is not significantly different from the control curve.

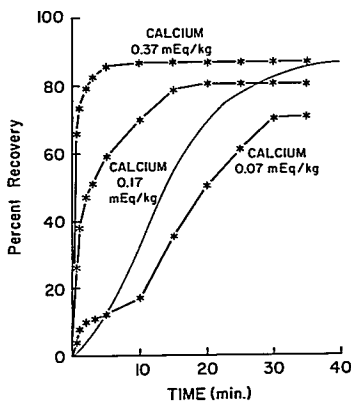


FIG. 6. Recovery from neomycin paralysis after administration of calcium. The doses shown are equivalent to one, three and seven ampoules of calcium gluconate administered to the average adult.

of parallelism of the dose-response curves, the group C curve being steeper than the group A or group B curves (fig. 2). A possible explanation is that at higher dose-depression levels the capacity of plasma protein to bind the two drugs has been exceeded. We did not attempt to clarify this mechanism.

Under the conditions of this experiment neostigmine did not antagonize neomycin paralysis effectively. Pittinger *et al.* showed that animals anesthetized with ether and given neomycin developed respiratory depression which was antagonized by neostigmine.⁵ None of Pittinger's animals were completely paralyzed, however, and neostigmine has been shown to be more effective in accelerating recovery in animals allowed to recover partially prior to its administration.⁷

Jones reported the first case in which administration of calcium produced reversal of respiratory depression associated with neomycin.⁸ He administered 200 mg of calcium gluconate to a 3-kg infant—equivalent to 0.3 mEq/kg of elemental calcium or 4.6 g of 10 per cent calcium gluconate to the average 70-kg adult. In our cats calcium, 0.37 mEq/kg, effectively accelerated recovery from neo-

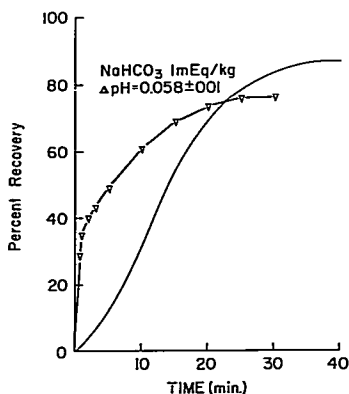


FIG. 7. Recovery from neomycin paralysis after administration of sodium bicarbonate.

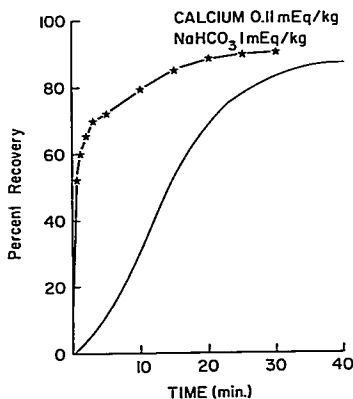


FIG. 8. Recovery from paralysis after administration of calcium and sodium bicarbonate.

mycin paralysis. However, equivalent recovery could not be achieved with lower doses of calcium unless sodium bicarbonate also was given.

Elnqvist and Josefsson have proposed two pharmacologic mechanisms for the neuromuscular blocking activity of neomycin: a) like curare, neomycin reduces the sensitivity of the postjunctional membrane to acetylcholine; b) neomycin inhibits release of acetylcholine from the neural endplate, an effect similar to those of low calcium or high magnesium concentration.⁹ Reversal of this blockade should be accomplished by antagonizing the curare-like effect with a cholinesterase inhibitor or by raising the calcium ion concentration.⁷ Neostigmine given alone is effective only when the block is incomplete, while calcium is effective with any degree of blockade. Our results show that sodium bicarbonate partially reverses complete neomycin neuromuscular block even in the presence of normal pH and blood gases. Furthermore, sodium bicarbonate enhances the recovery produced by a low dose of calcium. The mechanism of this effect is unclear.

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